

Serial No.: 10/749,602

Confirmation No.: 8548

Filed: December 31, 2003

For: IN OVO DELIVERY OF AN IMMUNOGEN CONTAINING IMPLANT

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### **Remarks**

The Office Action mailed May 13, 2008 has been received and reviewed. Claims 34-44, 67-69, 71-82, and 84-102 are pending. Claims 34, 69, and 84 are amended. Reconsideration and withdrawal of the rejections are respectfully requested.

### **Claim Amendments**

Claims 34, 69, and 84 are amended to recite methods of inducing adaptive immunity in a bird (with respect to claims 34 and 69) or a population of birds (with respect to claim 84) against a selected immunogen. Support for the amendments may be found in Applicants' disclosure at, for example, from page 22, line 7 through page 25, line 12.

### **Double Patenting Rejection**

Claims 34-44 and 67-69 stand rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-14 of U.S. Patent No. 6,682,754. Applicants respectfully traverse.

35 U.S.C. §121 states that a patent issuing on an application subject to a restriction requirement shall not be used as a reference either in the Patent and Trademark Office or in the courts against a divisional application or against the original application or any patent issued on either of them, if the divisional application is filed before the issuance of the patent on the other application.

Applicants respectfully submit the present application is a divisional application of U.S. Patent Application Serial No. 09/449,271 ("the parent application") and was filed on December 31, 2003, a date that is before the issuance of the parent application. Moreover, the rejected claims are based on nonelected claims identified in a restriction requirement, dated September 27, 2002 in the parent application, as being patentably distinct from the claims that were eventually allowed as claims 1-14 of U.S. Patent No. 6,682,754. Specifically, instant

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claims 34-40 correspond to claims 44 and 71-76 of Group I of the September 22, 2002 restriction requirement.

Applicants therefore respectfully submit that the rejection of claims 34-44 and 67-69 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-14 of U.S. Patent No. 6,682,754 is improper and request that the rejection be reconsidered and withdrawn.

### **The 35 U.S.C. §103 Rejection**

Claims 34, 37, 39-43, 67-69, 83-86, 89, 91-95, and 97-102 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Emery *et al.* (U.S. 5,830,479) in view of Phelps *et al.* (U.S. 5,339,766) in view of Genovese *et al.* (1998) in light of Sharma *et al.* (U.S. 4,458,630 A). Applicants respectfully traverse.

Claims 34, 69, and 84 are independent. Each of the remaining claims depends, directly or indirectly, from one of the independent claims. Thus, remarks that refer to one or more of the independent claims apply equally to any claim that depends from an identified independent claim.

M.P.E.P. §706.02(j) states, "To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art and not based on applicant's disclosure."

Applicants respectfully submit that the suggested combination of documents fails to establish a *prima facie* case of obviousness against claims 34, 69, and 84 because, at a minimum, the suggested combination of documents fails to provide motivation to make the

suggested combination. Also, the suggested combination of documents fails to provide one skilled in the art with a reasonable expectation of successfully practicing the methods recited in claims 34, 69, and 84.

Each of claims 34, 69, and 84 involves injecting a biocompatible implant into an egg or a population of eggs, in which the implant includes a selected immunogen and the egg (or eggs) possesses maternal antibody to the selected immunogen.

Emery *et al.* teach compositions that include siderophore receptor proteins (SRPs) and active immunization methods using such compositions. Emery *et al.* teach that such compositions may be delivered by, for example, egg inoculation (Emery *et al.*, col. 11, lines 9-16). However, Emery *et al.* provide no teaching relating to inoculating eggs possessing maternal antibody to the selected immunogen.

Thus, one important difference between the teaching of Emery *et al.* and the subject matter recited in claims 34, 69, and 84 is the nature of the eggs being inoculated. The subject matter of claims 34, 69, and 84 specifically recites that the eggs being inoculated possess maternal antibody to the selected antigen. Emery *et al.* provides no such teaching or suggestion. Consequently, in order for the rejection of claims 34, 69, and 84 to be proper, the motivation to inoculate eggs that possess maternal antibody to the selected antigen and a reasonable expectation that doing so will successfully induce adaptive immunity in birds hatching from the immunized egg (or eggs) must be provided in the combination of the secondary documents.

Phelps *et al.* teach methods of injecting substances into a bird egg (Phelps *et al.*, abstract) including, for example, vaccines (column 3, lines 33-36). The disclosure of Phelps *et al.* is generally related to the mechanical nature of injecting substances into the eggs—i.e., hatchability based on different methods of injection. Indeed, Phelps *et al.* provide no teaching relating to injecting substances into eggs possessing maternal antibody to a selected immunogen. Thus, Phelps *et al.* fail to cure the deficiencies of Emery *et al.* with respect to the methods recited in claims 34, 69, and 84.

Genovese *et al.* teach administering lymphokines to day-old turkeys in order to potentiate an innate immune response. Genovese *et al.* provide no teaching or suggestion of generating an adaptive immune response against a selected immunogen. Potentiation of an innate immune response and generation of an adaptive immune response occur through distinct mechanisms and are wholly unrelated. Thus, the knowledge that a method may be used to potentiate an innate immune response provides no predictive value for the ability of that same method to generate an adaptive immune response against a selected immunogen. Thus, Genovese *et al.* fail to cure the deficiencies of the combination of Emery *et al.* and Phelps *et al.* with respect to the methods recited in claims 34, 69, and 84.

Sharma *et al.* teach methods of controlling disease in avian species by embryonal vaccination (Sharma *et al.*, abstract). Sharma *et al.* recognize the effects of maternal antibodies on generating an adaptive immune response against non-cell associated vaccines—e.g., a vaccine of polypeptides as recited in Applicants' claims 34, 69, and 84 (column 3, lines 42-46). While Sharma *et al.* suggest two strategies for overcoming the effects of maternal antibodies on generating adaptive immunity against a selected immunogen (e.g., using a cell-associated vaccine and specifying an injection region), they do not demonstrate that these strategies are successful for protecting birds that hatch from eggs having maternal antibodies against the immunogen. Sharma *et al.* teach only immunizing eggs laid from hens naive to turkey herpes virus (HVT) with a cell-associated vaccine against HVT. Thus, Sharma *et al.* fail to teach or suggest immunizing eggs that possess maternal antibodies against a selected immunogen. Thus, Sharma *et al.* fail to cure the deficiencies of the combination of Emery *et al.*, Phelps *et al.*, and Genovese *et al.*

The Office Action asserts that Emery *et al.* and Phelps *et al.* provide motivation for the skilled artisan to inoculate eggs regardless of whether the egg would contain maternal antibodies to the selected immunogen “because there would be a reasonable expectation that the [*in ovo*] inoculation would have afforded the unhatched bird *some immunity to the antigen.*”

(Office Action, page 9, emphasis in original). The Office Action states at page 17, and then restates from page 18 to page 19, that the cited documents teach the following:

- 1) *In ovo* inoculation of SRPs was known;
- 2) *In ovo* inoculation with SRPs was specifically suggested to be carried out with sustained delivery agents;
- 3) Although maternal antibodies could potentially interfere with an immune response in a young, newly hatched bird, an immune response was nonetheless confirmed in birds *in ovo* as well as newly hatched chicks, and
- 4) A preferred time for inoculating birds was from 4-7 days.

Applicants respectfully submit that the position in the Office Action is unfounded and based on an incomplete consideration of the cited documents. Specifically, and at a minimum, Applicants respectfully submit that the cited documents do not establish generating an immune response either *in ovo* or in newly hatched chicks from vaccinated eggs possessing maternal antibodies against the vaccine immunogen. Also, the cited documents fail to establish that a preferred time for inoculating birds with a selected immunogen is at 4-7 days of age.

M.P.E.P. §2141.02(VI) states, "A prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984)." (emphasis in original).

With respect to item #3, the combination of documents must teach or suggest that an adaptive immune response can be induced in birds either *in ovo* or in newly hatched chicks or poults in order to be relevant to Applicants' claims 34, 69, and 84 as amended herein.

Applicants respectfully submit that the combination of documents fails to provide any such teaching or suggestion. As noted above, neither Phelps *et al.* nor Genovese *et al.* provide any teaching or suggestion relevant to inducing an adaptive immune response in eggs (or birds newly hatched from eggs) possessing maternal antibodies to a selected immunogen. Sharma *et al.* teach the measurement of HVT viral antigen at one day post-hatch in chicks vaccinated *in ovo*

ovo with a cell-associated HVT vaccine. (Sharma *et al.*, column 4, line 25 through column 5, line 3 and Table I). Importantly, the inoculated eggs were laid from hens naive to HVT and, therefore, the eggs could not have possessed maternal antibodies against any HVT antigen. (*Id.*, column 4, lines 25-34). Therefore, any apparent immune response reported in Sharma *et al.* is not predictive for the methods of claims 34, 69, and 84 because, in contrast to the claimed methods, the *in ovo* vaccinations were performed on eggs that do not possess maternal antibodies against the immunogen.

With respect to item #4, Genovese *et al.* teach potentiating an innate immune response by administering a lymphokine at 4-7 days. Genovese *et al.* do not teach “inoculating” birds at 4-7 days, as suggested in the Office Action, because “inoculating” requires administration of an antigen or disease-causing agent and Genovese *et al.* do not administer a disease-causing agent or antigen to the birds, as described more fully below.

Thus, there is no teaching or suggestion in the cited documents to support the position stated in the Office Action that one skilled in the art would have had a reasonable expectation that inoculating eggs possessing maternal antibody to an antigen in the vaccine would afford some immunity to the antigen in the vaccine. Moreover, there is no teaching or suggestion that such inoculation would afford adaptive immunity against the antigen in the vaccine. Those skilled in the art understood that maternal antibodies against selected immunogens compromised the ability of a poult or chick to mount its own immune response to the antigen. This understanding is confirmed in Sharma *et al.* (col. 3, lines 42-46). Nothing in Emery *et al.* or Phelps *et al.* overcomes this understanding.

The Office Action cites certain excerpts of Genovese *et al.* (Office Action, page 11-12), but taken as a whole, as is required by M.P.E.P. §2141.02(VI), Genovese *et al.* actually support patentability of the subject matter of claims 34, 69, and 84. Genovese *et al.* support Applicants’ repeated contention, dismissed throughout the Office Action, that one skilled in the art would not have expected administering an immunogen (e.g., an antigen) in the presence of

maternal antibodies to the immunogen—whether *in ovo* or after hatch—to provide adaptive immunological protection against the immunogen.

Part of the confusion may result from imprecise use of terminology in Genovese *et al.* in which the term “vaccination” refers both to compositions that elicit an innate immune response and compositions that induce an adaptive immune response. However, innate immunity and adaptive immunity are distinct immunological mechanisms. Genovese *et al.* are concerned with potentiating an innate response, while the subject matter of claims 34, 69, and 84 are concerned with inducing an adaptive immune response. Thus, while Genovese *et al.* use the term “vaccination” interchangeably between these two alternatives, giving the appearance of one method and or mechanism, Genovese *et al.* are, in reality referring to an immunological process that provides no predictive value for the unrelated immunological process involved in the methods recited in claims 34, 69, and 84.

The Office Action cites Genovese *et al.* as follows, “...it would be advantageous to administer an agent which could potentiate an immediate immune response for protection during the 4 to 7 days when the birds are most susceptible to these bacterial invaders and vaccination responses have not yet taken full effect.” (Office Action, page 11). This statement refers to potentiating an innate immune response to compensate for the lack of an adaptive immune response to antigens as a result of vaccination with bacterial antigens. Poults were injected with lymphokines derived from a virally-transformed chicken T cell line. Thus, the poults were not injected with an immunogen—i.e., the poults were not inoculated—and did not develop an adaptive immune response to any immunogen. Instead, the poults were injected with a lymphokine that upregulates immunogen-non-specific innate immunity.

Why do Genovese *et al.* try this approach to protecting poults against bacterial infection? Because, in the words of Genovese *et al.*, “the typical humoral/cell-mediated [i.e., adaptive] immune response requires 7 to 10 days to reach protective levels[.]” Genovese *et al.* continue with respect to immunogen-based vaccines, “In addition, maternal antibodies may cause interference with the vaccine and the desired immune response to that vaccine.” Thus,

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when Genovese *et al.* state, as cited in the Office Action, “vaccinations currently used on newly hatched chicks and poults do provide some levels of protection” (*Id.*), Genovese *et al.* teach, when read as a whole, that any such adaptive protection is not until 7 to 10 days after a newly hatched chick is vaccinated, thereby leaving a window of immunological vulnerability.

Genovese *et al.* seek to protect the newly hatched chicks during the window of immunological vulnerability by potentiating an immunogen-non-specific innate immune response. In contrast, Applicants provide protection during the window of immunological vulnerability by inducing an immunogen-specific adaptive immune response.

Each statement in Genovese *et al.* that the Office Action interprets as supporting the position that chicks and poults can generate a protective immune response in the first seven days of life refers to an innate immune response and is, therefore, wholly irrelevant and provides no predictive value relevant to the subject matter of claims 34, 69, and 84. Contrary to the apparent position set forth in the Office Action, Genovese *et al.* simply do not teach “inoculation” of chicks or poults with an immunogen or successful mounting of an adaptive immune response by newly hatched chicks or poults in the first seven days after hatching.

Consequently, what was clear to one skilled in the art at the time the invention was made was the following:

- 1) *In ovo* inoculation of SRPs was known;
- 2) *In ovo* inoculation with SRPs was specifically suggested to be carried out with sustained delivery agents;
- 3) Maternal antibodies against an immunogen can interfere with the induction of an adaptive immune response against the antigen in a chick or poult regardless of whether the chick or poult is vaccinated *in ovo* or after hatch; and
- 4) Therefore, while vaccination *in ovo* using a selected immunogen had been shown using eggs laid from hens naive to the selected immunogen, one skilled in the art would not have had a reasonable expectation that a similar inoculation of immunogen into an egg possessing

maternal antibodies against the immunogen would provide adaptive immunological protection *in ovo* or in newly hatched chicks or poults.

The Office Action argues along two lines. First, the Office Action argues that based on, for example, Emery *et al.*, one skilled in the art would be motivated to vaccinate eggs laid from each subsequent—and, presumably, non-naïve—generation (e.g., Office Action, page 9). Second, the Office Action argues that Genovese *et al.* teach that newly hatched chicks and/or poults can generate an immune response in the presence of maternal antibodies—i.e., at 4-7 days after hatch (e.g., Office Action, page 11). Both arguments are faulty.

One skilled in the art would not have been motivated to vaccinate eggs laid from subsequent—and, presumably, non-naïve—generation precisely because one skilled in the art understood that the presence of the maternal antibodies against the immunogen would interfere with induction of an adaptive immune response in the newly hatched chick. This concern is expressly acknowledged in Sharma *et al.* (column 3, lines 42-45) and Geneovese *et al.* (“In addition, maternal antibodies may cause interference with the vaccine and the desired immune response to that vaccine.”). The Office Action provides no meaningful rebuttal to this position.

The Office Action attempts to rebut this position based on the teaching of Genovese *et al.* As indicated above, Genovese *et al.* teach, however, the potentiation of an innate immune response 4-7 days after hatch when a lymphokine—not an immunogen, but a lymphokine—is administered to one-day-old turkey poults. Because Genovese *et al.* administer a lymphokine to induce an immunogen-non-specific innate immune response, this finding bears no relevance or predictive value to the claimed methods that involve inducing an immunogen-specific adaptive immune response against an administered immunogen.

Consequently, Applicants respectfully submit that none of the cited documents, and no combination of the cited documents, teaches or suggests immunizing eggs with a selected immunogen when the eggs possess maternal antibody against the antigen. As confirmed in, for example, Sharma *et al.* and Genovese *et al.*, maternal antibodies against a non-cell associated immunogen were known to interfere with the production of an adaptive immune response

against the immunogen. Thus, Sharma *et al.* suggest, for example, using cell-associated delivery of a virus—an approach inappropriate for delivery of SRPs—and Genovese *et al.* induced an innate immune response. Moreover, the suggested combination fails to provide one skilled in the art with a reasonable expectation that inoculating eggs with an immunogen would provide a protective adaptive immune response in a chick or poult hatching from the inoculated eggs.

Applicants therefore respectfully submit that claims 34, 37, 39-43, 67-69, 83-86, 89, 91-95, and 97-102 are patentable under 35 U.S.C. §103(a) over Emery *et al.* in view of Phelps *et al.*, in view of Genovese *et al.*, and in light of Sharma *et al.* and request that the rejection be withdrawn.

Claims 34-44, 67-69, 71-82, and 84-102 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Emery *et al.* (U.S. 5,830,479) in view of Phelps *et al.* (U.S. 5,339,766) in view of Evans *et al.* (U.S. 6,500,438 B2) in view of Genovese *et al.* (1998) in light of Sharma *et al.* (U.S. 4,458,630 A).

The teachings and deficiencies of Emery *et al.*, Phelps *et al.*, Genovese *et al.*, and Sharma *et al.* are provided in the immediately preceding section and will not be repeated in this section. Evans *et al.* teach immunizing chicken eggs with parasite sporozoites, sporocysts, and oocysts. Evans *et al.* fail to teach or suggest immunizing eggs that contain maternal antibodies against the selected sporozoite, sporocyst, or oocyst immunogens. Consequently, Evans *et al.* fails, at a minimum, to cure the primary deficiency of the combination of Emery *et al.*, Phelps *et al.*, Genovese *et al.*, and Sharma *et al.*

Applicants therefore respectfully submit that claims 34-44, 67-69, 71-82, and 84-102 are patentable under 35 U.S.C. §103(a) over Emery *et al.* in view of Phelps *et al.*, in view of Evans *et al.*, in view of Genovese *et al.* (1998) and in light of Sharma *et al.* and request that the rejection be withdrawn.

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**Summary**

It is respectfully submitted that the pending claims 34-44, 67-69, 71-82, and 84-102 are in condition for allowance and notification to that effect is respectfully requested. The Examiner is invited to contact Applicants' Representatives at the telephone number listed below if it is believed that prosecution of this application may be assisted thereby.

Respectfully submitted

By

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**CERTIFICATE UNDER 37 CFR §1.8:**

The undersigned hereby certifies that the paper(s), as described hereinabove, are being transmitted via the U.S. Patent and Trademark Office electronic filing system in accordance with 37 CFR §1.6(a)(4) to the Patent and Trademark Office addressed to Mail Stop AF, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on this 12th day of September, 2008.

By:

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